REMARKS

Status of the Claims

Presently, claims 1, 4, 6-23, and 29-34 are pending in the application. Claims 17-23 have been withdrawn as being drawn to a nonelected invention. Accordingly, claims 1, 4, 6-16, and 29-34 are under consideration.

Computer Program Listing

Applicants electronically submit herewith a .txt file containing a computer program listing appendix. The specification is amended herein to insert the reference to a computer program listing appendix. Pages 30-67 of the specification as filed that contained the computer program listing were cancelled in the amendment of October 17, 2006. Accordingly, Applicants believe the requirements of 37 CFR §1.96 have been met and respectfully request withdrawal of this objection.

Rejection of Claims 1, 4, 6-16, and 29-34 Under 35 USC §112, first paragraph

On pages 3-12 of the Official Action, claims 1, 4, 6-16 and 29-34 were rejected on the basis that the specification does not enable the use of the claimed compositions. Applicants respectfully traverse for the reasons set forth below. It would not require undue experimentation to use the claimed modified mRNA compositions as vaccines, in an art-recognized manner. As is clear from the background section of this application, the present invention is not directed to any particular use of the compositions *per se*, but rather, is drawn to compositions of specific nucleic acids (i.e. modified mRNAs) which can be used for vaccination, and which when so used avoid certain drawbacks associated with the prior art. See, for example, [0016] - [0018] of the specification.

Initially, it is noted that the rejection under 35 U.S.C. 112 is focused on the "how to use" aspect of enablement. The Office Action has recognized the sufficiency of the disclosure in terms of "how to make" the claimed compositions (Office Action, page 6, 1st full paragraph), and has focused on perceived insufficiency of the disclosure in relation to "how to use" the compositions.

The Office Action has focused upon the various utilities for the compositions which are disclosed in the specification, and the unpredictability associated with some of the envisioned utilities (in particular, gene therapy). While it is correct that the present application contemplates methods of gene therapy as embodiments of the invention, the subject claims now pending are product claims which recite a composition. The law is clear that, when a composition is being claimed, only a single disclosed use of the composition must be enabled in order for the enablement requirement of 35 U.S.C. 112 to be satisfied. See, e.g. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*65 U.S.P.Q. 2d 1385, 1400 and 1403 (Fed. Cir. 2003), citing *Johns Hopkins Univ. v. Cellpro, Inc.*, 47 USPQ2d 1705, 1719 (Fed.Cir.1998) and *Engel Indus. Inc. v. Lockformer Co.*, 20 USPQ2d 1300, 1304 (Fed.Cir.1991) (the specification need teach only one mode of making and using a claimed composition); see also, MPEP, 8th Ed., Section 2164.01(c), which provides, *inter alia*: "If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, ***if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention***." (emphasis added).

Applicants have disclosed that the compositions are useful as genetic vaccines. See e.g. [0051], [0052], [0060], [0061]. The use of the claimed compositions for vaccination is clearly enabled as of the effective filing date of this application.

A proper analysis of enablement takes into account the following relevant factors: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 8 U.S.P.Q. 1400 (Fed. Cir. 1988). Applicants therefore address the pertinent factors, and respond to the points noted by the Office Action relating to certain of these factors.

While the Examiner has focused upon certain statements in the cited articles to Dunham and Leitner et al. (Office Action, pp. 6-7), those same articles contain additional statements

suggesting a reasonably advanced and more mature "state of the art" in relation to genetic vaccination. For example:

> "In the past decade experimental DNA vaccines have been developed ***against many pathogens in many different species***. More recently, the concept has been extended further with the development of RNA vaccines (Hoerr et al. 2000)." Dunham, page 10, 1st column (emphasis added).[1]

> "Because genetic vaccines are relatively inexpensive and easy to manufacture and use, their immunogenicity and efficacy have been ***analyzed in a large number of systems and results from preclinical studies have supported human clinical trials***." Leitner et al, page 766, 1st column (emphasis added).

Specifically as to delivery:

> "Genetic vaccines can be delivered into the host by several routes and methods." Leitner et al, page 766, 1st column.

Moreover, the suggestion that a vaccine embodiment "must be optimized" for each target species - see Official Action, page 8, lines 1-4 - is not the correct standard for determining whether the required experimentation is "undue." Optimization of a particular, specific vaccine embodiment is within the skill of the art. Indeed, in the pharmaceutical arts, optimization of dosage and administration is almost always needed, and the need to optimize a particular embodiment is not a basis for finding nonenablement. See, e.g. *Merck and Co. Inc. v. Biocraft Laboratories, Inc.*, 10 U.S.P.Q. 2d 1843, 1847 (Fed. Cir. 1989)(finding that the experimentation needed to arrive at suitable dosages, though requiring time and care, is no more than routine).

The Office Action, at page 8, notes in particular the statement of page 766, right column of Leitner et al. that genetic vaccines in some systems have not proven satisfactory. But, that same paragraph goes on to state: "Some studies, however, purport that DNA vaccines are ***more efficacious*** than some established vaccines …" (emphasis added).

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[1] It is noted that Dr. Hoerr is a named inventor on the present patent application. The citation to "Hoerr et al. 2000" is a reference to the Dr. Hoerr's publication describing the use of RNA as a vaccine. Hoerr et al., Eur. J. Immun., 30: 1-7 (2000)(of record).

Also on page 8, the Examiner notes that, in relation to some diseases or cancer, the evidence suggests that genetic vaccines may not be therapeutically useful for vaccination of patients. Even assuming that is a correct characterization in relation to certain disease conditions, Applicants should not be held to a standard of enablement whereby proof of treatment or "cure" of any specific human condition must be demonstrated. That high standard is legally incorrect, and has been specifically held to confuse "the requirements for obtaining a patent with the requirements for obtaining government approval to market a particular drug." *In re Brana*, 34 U.S.P.Q. 2d 1436, 1441-42 (Fed. Cir. 1995).[2]

In discussing the *Wands* factors relating to "nature of the invention" (page 5, 2d full paragraph) and the "amount of experimentation necessary" (page 8, 1st full paragraph), the Examiner has focused on delivery of the modified mRNA. Delivery of the modified RNA in the composition of the invention is clearly enabled. Delivery of nucleic acids *in vivo* can be accomplished using art-recognized techniques. In addition, the specification cites to a known methodology involving direct injection. See [0061]. Lastly, the Declaration of Dr. Ingmar Hoerr, of record, illustrates "delivery" of the claimed RNA composition and attendant *in vivo* expression of the modified RNA and induction of an immune response.

Under "guidance of the specification" and "existence of working examples" the Examiner notes that no working examples demonstrating a therapeutic outcome are provided in the specification (it is noted, however, that actual making of modified mRNAs is disclosed).

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[2] The *Brana* decision cited with approval to the holding of the CCPA in *In re Krimmel*, 130 USPQ 215 at 219, which explained: "We hold as we do because it is our firm conviction that one has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans."

Usefulness in the patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention becomes useful is well before it is ready to be administered to humans. See, e.g. *Nelson v. Bowler*, 206 U.S.P.Q. 881, 883 (CCPA 1980)(stating, in the context of discussing the utility requirement of 35 U.S.C. 101, that the mere identification of a single pharmacological activity provides an immediate benefit to the public). See also MPEP 2107.03.

Applicants traverse that working examples showing vaccination are needed for enablement, and moreover, cite to the declaration of Dr. Hoerr which discloses a number of experiments demonstrative or predictive of vaccine utility.

It is well-established that a patent specification need not contain any working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue experimentation. *In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970); MPEP § 2164.02. Nothing more than objective enablement is required, which may be provided either through broad terminology or by illustrative examples. *In re Marzocchi*, 169 USPQ 367, 369-370 (CCPA 1971), and more recently, *Falkner v. Inglis*, 79 U.S.P.Q. 2d 1001 (Fed. Cir. 2006)(claims to a modified poxvirus vaccine were held enabled in the absence of working examples).

Supplementing the evidence in this case is the declaration of Dr. Hoerr, which provides evidence of enablement. All of the experimentation described in Dr. Hoerr's declaration was performed using the methodology described in the application as filed.[3]

In the "response to argument" section of the Official Action, the Office has criticized the sufficiency of the experiments reported in Dr. Hoerr's declaration. Applicants respond that the experiments confirm what is disclosed in the specification, and constitute evidence that legally-sufficient utility is enabled under the standards discussed above.

Applicants note that the Examiner's criticisms of the certain of the individual experiments are not entirely consistent with the position taken in the rejection. For example, as noted, the rejection is based, in part, on the perceived problem of nucleic acid delivery. Yet, certain of applicants' experiments are criticized on the basis of the selected antigen, and the choice of antigen is irrelevant to whether or not the modified mRNA was successfully delivered to the targeted cells/tissues. The reported experiments, together with the state of the art, clearly

[3] Enablement is judged as of the application filing date. A declaration containing further experimental evidence of utility, submitted after the filing date, is nonetheless relevant to substantiating a utility which has been described in the specification. *In re Brana*, 34 U.S.P.Q. 2d at 1441, note 19.

support a finding that "delivery" of a modified mRNA is within the grasp of a skilled artisan (while not discussed in the Office Action, it should be clear that the applicable level of ordinary skill in the relevant art is high).

Regardless of the choice of antigens, Applicants' experiments which are reported in Dr. Hoerr's declaration demonstrate that modified mRNA encoding an antigen can be delivered and expressed to produce an immune response. A skilled artisan would have expected that a genetic vaccine will generate an immune response. As noted, demonstration of successful therapy in a human subject is not the applicable legal standard (although it should be noted that Dr. Hoerr's declaration does evidence successful delivery of modified mRNA in human subjects, and thus goes beyond the amount of evidence minimally required to prove enablement). In view of evidence showing, e.g., that the modified mRNAs of the claimed compositions are more stably expressed than "wild-type" mRNA, the skilled artisan would have no objective basis to doubt enablement, and would view the reported experiments as confirming enablement and utility.

To summarize on enablement, the present application need only enable one disclosed utility of the claimed compositions (e.g. use of the composition for genetic vaccination). A proper *Wands* analysis in this case weighs strongly in favor of enablement, since the prior art generally enables the practice of genetic vaccination. The present invention is useful, *inter alia*, as an improvement in existing genetic vaccine technology, by providing as the genetic component of the composition a more highly-expressed, modified mRNA.

For these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph is requested.

CONCLUSION

In view of the foregoing remarks, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee is due with this response except as provided for elsewhere in this response. However, if any fee is due, please charge our Deposit Account No. 22-0185, under Order No. 22122-00009-US1 from which the undersigned is authorized to draw.

Dated: January 28, 2008

Respectfully submitted,

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